Usefulness of Radial Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Mediastinal Lymph Nodes

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ABSTRACT

Introduction: Transbronchial needle aspiration (TBNA) is a bronchoscopic technique that has been shown to be useful for sampling mediastinal lymph nodes. The yield of this technique can be increased by using endobronchial ultrasound (EBUS) to guide needle placement. The aim of the present study was to compare the yield of EBUS-guided TBNA to that of conventional TBNA in the analysis of mediastinal lymph nodes.

Patients and Methods: All patients undergoing either EBUS-guided or conventional TBNA for the diagnosis of mediastinal lymph nodes between January 2006 and May 2007 were studied consecutively. Histology results were used as a reference standard in patients treated surgically. In cases in which surgery was not indicated, the results of cytology or of clinical follow-up of at least 6 months duration were used.

Results: TBNA was performed in 117 patients and a total of 143 lymph nodes were punctured (mean shortest [SD] diameter, 17.9 [8] mm). The samples obtained were diagnostic in 58 patients (49.6%) and in 70 lymph nodes (49.0%). For paratracheal and hilar stations, the yield of EBUS-guided TBNA was superior to that of conventional TBNA (59.2% compared to 34.1%, P<.02).

Conclusions: Radial EBUS guidance increases the diagnostic yield of TBNA in paratracheal and hilar lymph node stations.

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Introduction

The prognosis of lung cancer, the most common cause of cancer death, depends mainly on the stage of the disease at diagnosis. For this reason an accurate assessment of the extent of disease is essential in order to determine the best therapeutic option for each patient. For the staging of non-small cell lung cancer, the TNM classification is used, and the evaluation of enlarged mediastinal lymph nodes is a fundamental part of the process.

Mediastinoscopy, with a sensitivity of 80% to 85% and a specificity of nearly 100%, is considered the gold standard test for mediastinal lymph node evaluation. However, it does not allow access to all lymph node stations, requires hospitalization and general anesthesia, is costly, and is associated with a rate of morbidity that is not insignificant. This situation has led to the promotion in recent years of minimally invasive techniques for mediastinal staging in patients with lung cancer. Transbronchial needle aspiration (TBNA) is a bronchoscopic technique used to obtain cytology and histology samples of lesions adjacent to the tracheobronchial tree. Its yield, however, is quite variable, with a sensitivity ranging from 37% to 72%, and a specificity of nearly 100%.

To a large extent, this variability in sensitivity is due to the fact that TBNA is often performed blindly, using only computed tomography (CT) images to determine the puncture site. Radial endobronchial ultrasound (EBUS) is a new technique that combines endoscopic visualization with high frequency ultrasound imaging. This makes it possible to obtain simultaneous images of the various layers of the bronchial wall as well as of the mediastinum and structures adjacent to the bronchus. All of this makes it easier, for example, to locate the lymph nodes to be sampled. In some studies, the sensitivity of radial EBUS-guided TBNA ranged from 67% to 85%, with a diagnostic accuracy of 86% to 98%.

The main aim of our study was to evaluate the usefulness of EBUS-guided TBNA in obtaining cytologic diagnosis of mediastinal lymph nodes compared to the results obtained with conventional TBNA. We also analyzed the advantages and limitations of this technique, which has only recently begun to be applied in Spain.

Patients and Methods

We studied consecutively all the patients who underwent TBNA for the evaluation of enlarged mediastinal lymph nodes between January 2006 and May 2007. We evaluated the yield of radial EBUS-guided TBNA and then compared it to that of conventional (blind) TBNA. In patients with suspected lung cancer undergoing TBNA for mediastinal staging, the technique was performed during the diagnostic bronchoscopy of the tumor. The patients were divided into 2 groups: radial EBUS-guided TBNA and conventional TBNA. As our respiratory endoscopy unit had an anesthesiologist available only 1 day per week, radial EBUS-guided TBNA was scheduled for that day, while conventional TBNA was performed on the remaining days. TBNA was performed on those hilar and/or mediastinal nodes with a short-axis diameter of 10 mm or more as determined by computed tomography (CT). Using images obtained with a multidetector CT scanner (Sensation 4, Siemens, Erlangen, Germany) after intravenous administration of 115 mL of contrast medium (Ioversol, Optiray 300 Ultraject, Tyco Healthcare, Sant Joan Despí, Spain), we calculated the short-axis (A) and long-axis (B) diameters of the lymph nodes in the axial plane (standard measures) and the ratio of the 2 diameters (A to B). We also measured diameter Y, parallel to the direction of needle insertion, and diameters X and Z, perpendicular to the direction of needle insertion, in order to analyze whether these measurements could be useful in predicting TBNA yield (Figure 1).

Procedure

Bronchoscopy was performed in the respiratory endoscopy unit following premedication with sublingual diazepam and the administration of 2% lidocaine as topical anesthesia. In patients undergoing radial EBUS-guided TBNA, fiberoptic bronchoscopy was performed under sedation with intravenous propofol and remifentanil, supervised by an anesthesiologist. In the rest, intravenous midazolam was administered at the discretion of the bronchoscopist. Olympus fiberoptic bronchoscopes (BF P200, 200, and BF 1T160; Olympus, Tokyo, Japan) were used. All procedures were performed by a single bronchoscopist after obtaining informed consent from the patient and ascertaining that coagulation parameters were acceptable (platelet count >60 000/μL and prothrombin time >60%).

Transbronchial Needle Aspiration

In order to minimize contamination of the working channel by malignant cells, TBNA was carried out before any other diagnostic technique was used. In no case was there neoplastic infiltration of the mucosa in the area to be punctured. We used 22-gauge cytology needles (MW-222, Bard, Billerica, Maine, USA). Generally, from 3 to 4 punctures were performed for each node station evaluated. The aspirates were then smeared on slides and immersed in 96% alcohol in preparation for subsequent cytology. In the pathology laboratory they were stained with conventional Papanicolaou stain. The
Results

A total of 117 patients (96 [82%] men) with a mean age of 63.8 (12.8) years were enrolled, and a total of 143 mediastinal lymph nodes were punctured. The lymph node stations evaluated, using the anatomic system described by Wang, were lower paratracheal (4R and 4L) in 19 cases (26%), subcarinal (7) in 32 cases (44%), hilar (10R and 10L) in 22 cases (30%) for conventional TBNA, and 26 (37.2%), 21 (30%), and 23 (32.9%), respectively, for radial EBUS-guided TBNA. There were no significant differences between the 2 groups in the mean size (short-axis diameter) of the enlarged lymph nodes detected by CT (17.9 [8] mm) or in the lymph node stations evaluated (Table 1).

The material obtained by TBNA was adequate and diagnostic in 58 (49.6%) of the 117 patients, and in 70 (49.0%) of the 143 lymph nodes sampled. The definitive diagnosis was tumor infiltration in 77 (65.8%) patients. Malignancy was ruled out in the rest (34.2%). In 10 (13%) of the 77 cases of lung cancer, TBNA was the only technique that allowed the diagnosis to be made.

The cytologic diagnoses obtained with TBNA are shown in Table 1. Conventional TBNA was used in 73 (51%) of the lymph nodes sampled and radial EBUS-guided TBNA in 70 (49%). The short-axis diameters of benign and malignant nodes were not significantly different (16.4 [5] and 18.3 [9] mm, respectively). No relationship was observed between the size of the nodes studied (calculated on the basis of the diameters measured by the radiologist using the CT images) and either TBNA yield or the presence or absence of malignancy.

Conventional TBNA was diagnostic in 73 (43.8%) of the punctures and radial EBUS-guided TBNA in 70 (54.3%) (P value not significant).

Table 1

<table>
<thead>
<tr>
<th>Characteristics of Study Population</th>
<th>Without EBUS</th>
<th>With EBUS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>62</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>65.7 (13.4)</td>
<td>61.5 (12.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Short-axis lymph node diameter, mm</td>
<td>17.4 (8.3)</td>
<td>18.2 (7.8)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of lymph nodes sampled</td>
<td>73</td>
<td>70</td>
<td>NS</td>
</tr>
<tr>
<td>Station 4 right paratracheal</td>
<td>15 (20.5%)</td>
<td>20 (28.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Station 4 left paratracheal</td>
<td>4 (5.5%)</td>
<td>6 (8.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Station 7 subcarinal</td>
<td>32 (44.0%)</td>
<td>21 (30.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Station 10 right hilar</td>
<td>19 (26.0%)</td>
<td>20 (28.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Station 10 left hilar</td>
<td>3 (4.0%)</td>
<td>3 (4.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Anatomically abnormal lymph nodes</td>
<td>73</td>
<td>70</td>
<td>NS</td>
</tr>
<tr>
<td>Normal lymph nodes</td>
<td>17 (23.3%)</td>
<td>24 (34.3%)</td>
<td></td>
</tr>
<tr>
<td>Neoplastic cells</td>
<td>14 (19.1%)</td>
<td>12 (17.1%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>4 (5.5%)</td>
<td>6 (8.5%)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3 (4.1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>4 (5.5%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Small cell lung carcinoma</td>
<td>1 (4.1%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1 (4.1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (1.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Granuloma</td>
<td>1 (1.4%)</td>
<td>2 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Inadequate sample</td>
<td>41 (56.2%)</td>
<td>32 (45.7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: EBUS, endobronchial ultrasound; NS, not significant.

*Data are presented as mean (SD) or number (%).
The present study shows that the diagnostic yield of radial EBUS-guided TBNA is superior to that of conventional TBNA for the study of enlarged lymph nodes in the lower paratracheal and hilar regions. Conventional TBNA is a bronchoscopic technique with a diagnostic yield that is still quite variable. While known to most pulmonologists, it is still underused at the present time. One reason for this underuse is the steep learning curve required of the bronchoscopist. Another is the fact that it is a blind technique and consequently smaller nodes in less accessible locations are difficult to reach with it. There are also several possible explanations for the variability of the results. It is well known that the yield of TBNA in patients with cancer depends on the prevalence of mediastinal metastases in the study population. For a prevalence of 25%, for example, the sensitivity is approximately 40%, while it can be as high as 80% for a prevalence of 80%. The type of needle used is another factor to be taken into account. Several studies show an increase in yield when 19-gauge needles are used. The site, size, and benign or malignant nature of the lymph node also affects TBNA yield. However, certain strategies can increase the yield of the technique. It is recommended, for example, that 4 needle passes be made at each station to be punctured. A number greater than 7 increases examination time and the risk of damaging the bronchoscope. The possibility of having the cytopathologist evaluate the sample on site—known by the acronym ROSE (rapid on-site evaluation)—increases yield considerably. Unfortunately, the availability of a cytopathologist for ROSE is not within the reach of most hospitals.

The option of using TBNA under CT guidance has not become widespread. The problem here is not so much the exposure of the patient and health care professionals to radiation, as the logistic (occupation/utilization of the CT room) and ergonomic (position of the bronchoscopist with respect to the patient on the CT table) difficulties involved. Finally, perhaps the most important factor is the experience of the bronchoscopist. Some studies have reported a considerable increase in TBNA yield over periods of 2 to 3 years.

In recent years, endoscopic ultrasound techniques to guide needle aspiration have been introduced. The first such technique to be introduced was endoscopic ultrasound-guided fine needle aspiration, which makes it possible to reach paratracheal, aortopulmonary window, subcarinal, and paraesophageal nodes. This technique, which combines digestive endoscopy with ultrasound-guided needle aspiration, has been shown to be effective in the diagnosis of mediastinal lymph nodes. Later, radial EBUS-guided and, more recently, real time EBUS-guided TBNA were introduced. Radial EBUS makes it possible to visualize the peribronchial structures during bronchoscopy and is extremely helpful in locating lymph nodes in the mediastinal area. It is a minimally invasive procedure that requires neither general anesthesia nor hospitalization, and no complications of note have been reported in any of the studies published to date. In our study, the first to analyze the results obtained with radial EBUS in Spain, we found that while this technique did prolong examination time, TBNA yield was significantly increased for all but the subcarinal station. This was consistent with the findings in the first 2 studies published by Herth et al. In this respect, it differs from conventional TBNA, in which there are significant differences in yield depending on the location and size of the lymph node.

A learning curve, as yet undefined, is required for the puncture technique and for the interpretation of the ultrasound images. While some authors have reported that at least 50 procedures are needed before the technique can be said to have been mastered, the number of procedures needed for the correct interpretation of images of the mediastinum obtained using radial EBUS has not yet been established. This is a new technique, and a potential criticism of our results is the possible effect of the limited experience of the bronchoscopist. However, before the beginning of the study, the bronchoscopist underwent a 5-month period of training and practice at a specialized center (Thoraxklinik, Heidelberg, Germany) under the direct supervision of experts. Nonetheless, the yield achieved in the first 70 radial EBUS-guided TBNA procedures and in conventional TBNA procedures in our hospital was lower than in other studies. This may be due to the fact that these other studies were carried out in specialized centers with extensive experience with TBNA. We can infer from this that the period analyzed in the present study reflected that part of the learning curve in which the technique is consolidated, and we can thus hope that results will improve after a greater number of procedures have been performed.

The trend towards a greater yield in blind TBNA in the subcarinal station can be attributed to a type II (sample size) error. It is true, however, that studies with larger numbers of patients have shown

### Table 2

<table>
<thead>
<tr>
<th>Lymph Node Station 7</th>
<th>Radial EBUS-Guided TBNA</th>
<th>Conventional TBNA</th>
<th>P</th>
<th>Lymph Node Stations 4R, 4L, 10R, and 10L</th>
<th>Radial EBUS-Guided TBNA</th>
<th>Conventional TBNA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of TBNA procedures</td>
<td>32</td>
<td>21</td>
<td></td>
<td>41</td>
<td>49</td>
<td>34.1</td>
<td>NS</td>
</tr>
<tr>
<td>Short-axis diameter of enlarged node, mm*</td>
<td>15 (4)</td>
<td>19.6 (7)</td>
<td>NS</td>
<td>19.1 (10)</td>
<td>17.6 (7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Yield, %</td>
<td>56.2</td>
<td>43.0</td>
<td></td>
<td>34.1</td>
<td>59.2</td>
<td>59.2</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: EBUS, endobronchial ultrasound; NS, not significant; TBNA, transbronchial needle aspiration.

*Mean (SD)
that radial EBUS offers no advantages over conventional TBNA in the evaluation of subcarinal lymph nodes.\textsuperscript{11,15} In our study, the results obtained in the subcarinal station may have been a factor in the lack of difference between the 2 groups in overall TBNA yield. The diagnostic yield we achieved with conventional TBNA was somewhat lower than that obtained in other Spanish studies.\textsuperscript{17,21,25} One possible reason for this is that we did not include the samples that were inadequate for cytological analysis in the calculation of the sensitivity and specificity of the technique. Furthermore, the prevalence of lymph node metastases in the sample analyzed was 57%, a lower percentage than that found in other studies.\textsuperscript{17,25} Thus, the yield we obtained is probably an expected result for this prevalence and comparable to that found by other authors.\textsuperscript{16}

While TBNA yield can be improved, positive TBNA rendered mediastinoscopy unnecessary in 32 cases in our series, thereby reducing morbidity, the interval between consultation and start of treatment, and the financial cost of diagnosis and staging. It is noteworthy that in recent years, since the introduction of TBNA, the number of extended cervical mediastinoscopies performed in our hospital has decreased continuously (25 in 2005, 15 in 2006, and 6 in 2007).

The time required for ultrasound detection and subsequent puncture of lymph nodes in our study was about 15 minutes, as compared to the approximately 6 minutes reported by Herth et al.\textsuperscript{11} Once again, the differences can be explained by the far greater accumulated experience of the Heidelberg group.

In CT, a morphologic criterion has traditionally been used to predict malignancy in enlarged mediastinal lymph nodes. Lymph nodes with a short-axis diameter greater than 10 mm in paratracheal and hilar regions and greater than 12 mm in the subcarinal region, and those with a shortest-to-longest diameter ratio of more than 0.7 are considered abnormal.\textsuperscript{26} In our study we also studied the relationship between lymph node diameters as measured by CT and TBNA yield. In contrast to the findings of Fernández-Villar et al.,\textsuperscript{11} we found no association between TBNA yield and the diameters usually measured. While a better TBNA yield would be expected in nodes with a longest diameter parallel to the direction of needle insertion (Y) and longest diameters perpendicular to the direction of needle insertion (X and Z), this was not the case in our study, probably because of the narrow range of diameters in the nodes analyzed.

The possible limitations of our study are those characteristic of any study based on clinical practice. Thus, there was no surgical confirmation of positive TBNA findings. However, several studies have shown that false positives are rare when measures are taken to avoid the contamination of the fiberoptic bronchoscope and strict cytologic criteria are used.\textsuperscript{17,23}

EBUS with real-time TBNA is a technique that has shown greater sensitivity than radial EBUS for the diagnosis of mediastinal lymph nodes, as it allows access to nodes that are small and hard to reach.\textsuperscript{27,28} An additional advantage of EBUS with real-time TBNA is that the technique can be mastered with acceptable results in a shorter time than that required for radial EBUS. There is an advantage, however, to using radial EBUS in patients with suspected lung cancer—the mediastinal lymph nodes can be sampled during the diagnostic bronchoscopy, thus shortening the time needed for diagnosis and staging as well as reducing the costs of the procedure. Since radial EBUS uses a conventional video bronchoscope, the financial investment by the respiratory endoscopy department is limited to the cost of the ultrasound miniprobe and processor. The cost is therefore lower than for EBUS with real-time TBNA, which requires an ultrasound bronchoscope, a processor, and an echograph. Another advantage of radial EBUS is that, as well as being a useful instrument for locating enlarged mediastinal nodes, it allows greater accuracy in the diagnosis of the local spread of tumors, as it evaluates whether or not there has been infiltration of mediastinal structures such as the esophagus, trachea, aorta, vena cava, and pulmonary artery.\textsuperscript{29} Finally, the usefulness of radial EBUS for detecting peripheral pulmonary lesions with greater accuracy than fluoroscopy has been demonstrated. It thus also reduces the exposure of the patient and health care professionals to radiation.\textsuperscript{30,31}

In summary, our study showed that radial EBUS guidance increases the diagnostic yield of TBNA in paratracheal and hilar node stations and renders mediastinoscopy unnecessary in a considerable number of patients.

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References

26. Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm) lymph node lesions. Chest. 2000;117:773-8.


